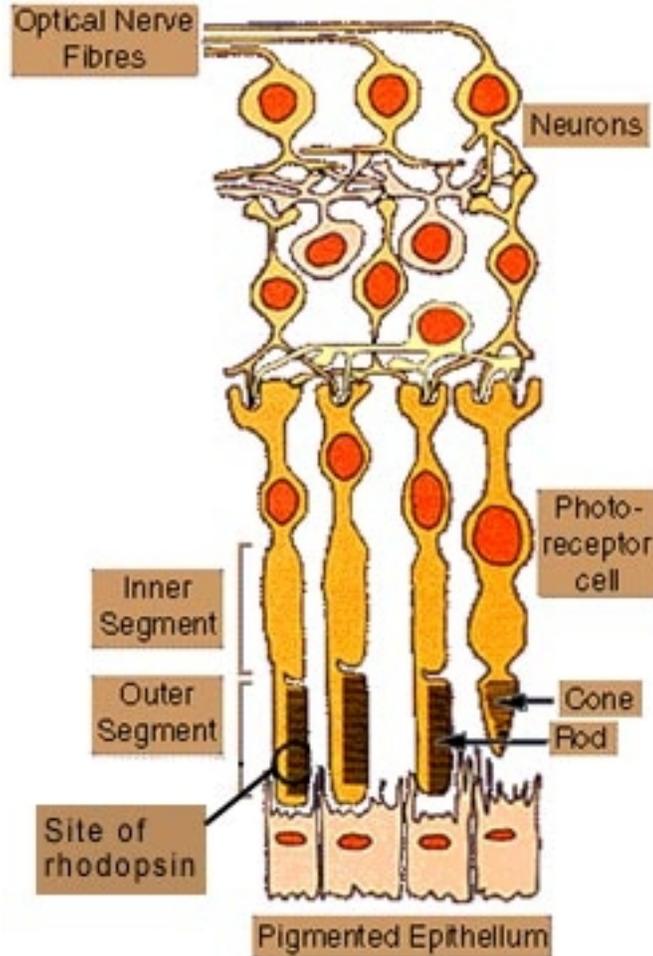


Diseases of the Eye



In the eye, light enters the pupil, is focused and inverted by the cornea and lens, and then is projected onto the retina at the back of the eye. The retina consists of several layers of cells, shown above. The only light-sensitive step during vision takes place in the outer segment of photoreceptor cells, and is catalysed by the molecule rhodopsin. Light causes rhodopsin to change shape, which then triggers a signal to be sent through the layers of cells that make up the retina, resulting in a neural signal to the brain. (Adapted from Gebhard Schertler's web page, MRC-LMB, Cambridge, UK, with permission.)

The function of our eyes is to allow us to see the objects in our surroundings at variable distances and under various conditions of lights. This function is achieved by a very complex arrangement of layers and structures found in the eye. In addition, two pockets of transparent fluid — the aqueous and vitreous humors — nourish eye tissues and help maintain constant eye shape.

The eye is comprised of three layers: an outer protective white coating called the sclera; a middle layer (choroid) containing blood vessels which nourish the eye; and an inner layer (retina) which contains the nerves that bear information to the brain for processing.

The cornea is the clear portion found at the front of the eye and serves to bend light rays. The iris, an extension of the choroid, is the colored portion of the eye and is made up of a spongy tissue. The pupil (black) is an opening in the iris that allows light into the eye. The lens then helps focus the light rays onto photoreceptors, which absorb and convert the light into electrical signals that carry information. The optic nerve contains fibers that transmit these signals to the brain for interpretation of the objects seen.

With the recent advances in molecular genetic techniques, new genes that cause eye disease are rapidly being identified, such as for those diseases discussed here. In many instances, these findings allow researchers to develop innovative strategies for preventing or slowing the progress of genetic eye diseases.

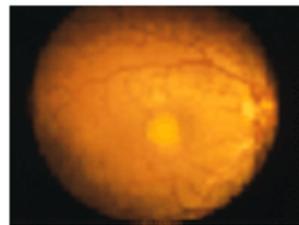
Best disease

Best disease, also known as Vitelliform Macular Dystrophy type 2 (VMD2), is a heritable disorder occurring primarily in European Caucasians. Individuals with Best disease generally show a gradual loss of visual acuity starting in their teenage years, although the frequency with which an affected individual may show symptoms and the severity of those symptoms are highly variable.

Best disease is autosomal dominant; in other words, a mutation in only one copy of the VMD2 gene located on chromosome 11 may result in development of the disease. Prior to their vision loss, individuals with Best disease accumulate a mass of fat-like material that resembles an egg yolk (vitelline is a word that means yolk-like) in the area of the retina responsible for central vision. Surprisingly, it is the breakup of this mass rather than its formation that is associated with the gradual vision loss characteristic of Best disease.

Little is known about the protein product of the VMD2 gene, although its function seems to be restricted to an area of the eye known as the retinal

pigment epithelium. There is speculation that the protein encoded by VMD2 may be involved in the removal and/or processing of photoreceptor components. Determination of the VMD2 protein function and development of an animal model will be the next crucial steps toward a better understanding of Best disease.



Photograph of an eye from a patient with Best disease. Note the mass of lipid-like material in the macular region.

[Reproduced from Marquardt, A. *et al.* (1988) *Human Molecular Genetics* 7(9): 1517-25, with permission.

Important Links

Gene sequence

Genome view see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=Vitelliform%20Macular%20Dystrophy&ORG=Hs&V=0] collection of gene-related information

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4759310&org=1] related sequences in different organisms

The literature

Research articles online full text

Books online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=153700] catalog of human genes and disorders

Websites

Foundation Fighting Blindness [www.blindness.org/html/about/wabout.html] searching for treatments and cures for retinal degenerative diseases

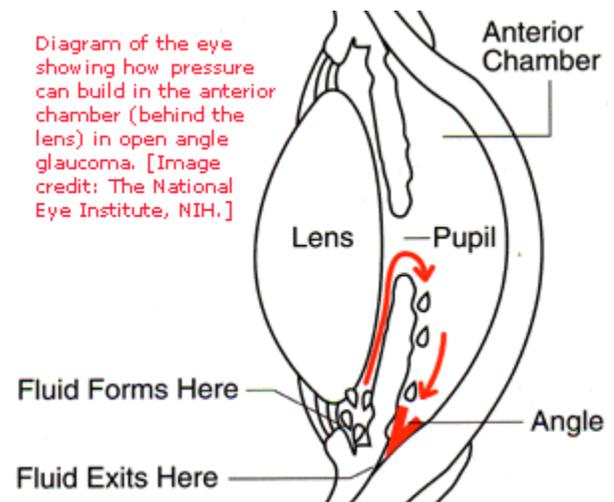
Glaucoma

"Glaucoma" is a term used for a group of diseases that can lead to damage to the eye's optic nerve and result in blindness. The most common form of the disease is open-angle glaucoma, which affects about 3 million Americans, half of whom don't know they have it. Glaucoma has no symptoms at first but over the years can steal its victims' sight, with side vision being affected first.

It is estimated that nearly 100,000 individuals in the US suffer from glaucoma due to a mutation in the *GLC1A* gene, found on chromosome 1. There has been some speculation as to the role of the gene product in the eye. As it is found in the structures of the eye involved in pressure regulation, it may cause increased pressure in the eye by obstructing the aqueous outflow.

With early treatment, serious loss of vision and blindness can be prevented. The cloning of the *GLCA1* gene is the first step toward an understand-

ing of the pathology of glaucoma at the molecular level and may help in the development of tests for the early detection of the disease, as well as providing a basis for research into effective therapies.



Important Links

Gene sequence

Genome view see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=glaucoma&ORG=Hs&V=0] collection of gene-related information

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=455777&org=1] related sequences in different organisms

The literature

Research articles online full text

Books online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=137750] catalog of human genes and disorders

Websites

Fact sheet [http://www.nei.nih.gov/health/glaucoma/glaucoma_facts.htm] for patients and the public from the National Eye Institute, NIH

The Glaucoma Foundation [www.glaucoma-foundation.org/info/] an international not-for-profit organization

The Glaucoma Research Foundation [www.glaucoma.org/] a US national not-for-profit organization

Gyrate atrophy of the choroid and retina

People suffering from gyrate atrophy of the choroid (the thin coating of the eye) and retina face a progressive loss of vision, with total blindness usually occurring between the ages of 40 and 60. The disease is an inborn error of metabolism.

The gene whose mutation causes gyrate atrophy is found on chromosome 10, and encodes an enzyme called ornithine ketoacid aminotransferase (OAT). Different inherited mutations in OAT cause differences in the severity of symptoms of the disease. OAT converts the amino acid ornithine from the urea cycle ultimately into glutamate. In gyrate atrophy, where OAT function is affected, there is an increase in plasma levels of ornithine.

It is already known that reduction of the amino acid arginine in the diet has a salutary effect on most patients. Current lines of research into the disease include: (1) investigating how variant mutations of the alleles (versions of the gene inherited)

interact in order to cause the differing symptoms of the disease and (2) work on mouse models of the disease is furthering our understanding, which is hoped will lead to a true cure.



The retina of a patient with gyrate atrophy of the choroid and retina of the eye caused by ornithine aminotransferase (OAT) deficiency. [Image credit: Muriel Kaiser-Kupfer, NEI, NIH, Bethesda, MD, USA and David Valle, Johns Hopkins University, Baltimore, MD, USA.]

Important Links

Gene sequence

Genome view see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=gyrate+atrophy&ORG=Hs&V=0] collection of gene-related information

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557809&org=1] related sequences in different organisms

The literature

Research articles online full text

Books online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=258870] catalog of human genes and disorders

Websites

Eye News Online [www.eye-news.com/vol3_6.dir/review/16rev3_5l.htm] containing information on gyrate atrophy

The National Eye Institute [www.nei.nih.gov/] research and information

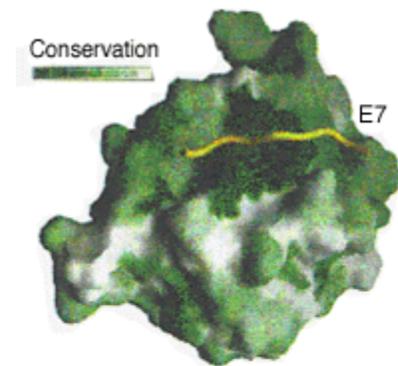
Retinoblastoma

Retinoblastoma occurs in early childhood and affects about 1 child in 20,000. The tumor develops from the immature retina - the part of the eye responsible for detecting light and color. There are both hereditary and non-hereditary forms of retinoblastoma. IN the hereditary form, multiple tumors are found in both eyes, while in the non-hereditary form only one eye is effected and by only one tumor.

In the hereditary form, a gene called Rb is lost from chromosome 13. Since the absence of Rb seemed to be linked to retinoblastoma, it has been suggested that the role of Rb in normal cells is to suppress tumor formation. Rb is found in all cells of the body, where under normal conditions it acts as a brake on the cell division cycle by preventing certain regulatory proteins from triggering DNA replication. If Rb is missing, a cell can replicate itself over and over in an uncontrolled manner, resulting in tumor formation.

Untreated, retinoblastoma is almost uniformly fatal, but with early diagnosis and modern methods of treatment the survival rate is over 90%. Since the

Rb gene is found in all cell types, studying the molecular mechanism of tumor suppression by Rb will give insight into the progression of many types of cancer, not just retinoblastoma.



A complex of retinoblastoma protein (RB) with E7 - a viral oncoprotein that frequently binds to RB and blocks its function in cervical cancer. The degree of green color shows the conservation of amino acids in RB and related proteins. [Reproduced from Lee, J-O., Russo, A.A. and Pavletich, N.P. (1998) Nature 391, 859-865, with permission.]

Important Links

Gene sequence

Genome view see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=RB1&ORG=Hs&V=0] collection of gene-related information

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4506435&org=1] related sequences in different organisms

The literature

Research articles online full text

Books online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=180200] catalog of human genes and disorders

Websites

The National Eye Institute, NIH [www.nei.nih.gov/] research and patient information